Attorney's Docket No. 35800/204489(5800-28A) PATENT

RESPONSE UNDER 37 C.F.R. 1.116 - EXPEDITED PROCEDURE - EXAMINING GROUP 1655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Robison et al.	Confirmation No.:	9505
Appl. No.:	09/668,266	Group Art Unit:	1655
Filed:	September 22, 2000	Examiner:	B. Sisson
For:	22025, A NOVEL HUMAN CYCLIC NUCLEOTIDE PHOSPHODIESTERASE		

November 20, 2001

BOX AF
U.S. Patent and Trademark Office
P. O. Box 2327
Arlington, VA 22202

AMENDMENT AFTER FINAL ACTION
PURSUANT TO 37 C.F.R. § 1.116

Sir:

Responsive to the Final Office Action of August 21, 2001, Applicants respectfully request reexamination and reconsideration of the above-identified application in view of the following amendments and remarks.

The Examiner is respectfully requested to enter the following amendments.

In the Claims:

Please cancel claims 2-18, 20, 22-28, 31, and 36-43 without prejudice to or disclaimer of the subject matter contained therein. Claims 2-18, 22, 25, 28, 31, 36-40, 42, and 43 are cancelled as being drawn to the non-elected invention.

Please amend claims 19, 29, and 32-34 to read as follows:

19. (Amended) An isolated polypeptide having an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence set forth in SEQ ID NO:1;

C1 cont.

(b) the amino acid sequence set forth in SEQ ID NO:3; and

(c) the amino acid sequence encoded by the cDNA insert contained in ATCC Patent Deposit No. PTA-1644.

C2

29. (Amended) A polypeptide having a phosphodiesterase activity, wherein said polypeptide is encoded by a nucleotide sequence selected from the group consisting of:

a) a nucleotide sequence having at least 80% sequence identity to the nucleotide sequence set forth in SEQ ID NO:2; and

b) a nucleotide sequence having at least 80% sequence identity to the nucleotide sequence set forth in SEQ ID NO:4.

32. (Amended) The polypeptide of claim 29 wherein said polypeptide is encoded by a nucleotide sequence selected from the group consisting of:

a) a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:2; and

b) a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:4.

C3

33. (Amended) The polypeptide of claim 32 wherein said polypeptide is encoded by a nucleotide sequence selected from the group consisting of:

a) a nucleotide sequence having at least 95% sequence identity to the nucleotide sequence set forth in SEQ ID NO:2; and

b) a nucleotide sequence having at least 95% sequence identity to the nucleotide sequence set forth in SEQ ID NO:4.

34. (Amended) A polypeptide having phosphodiesterase activity, wherein the polypeptide is encoded by a nucleic acid molecule that hybridizes to the cDNA insert contained in ATCC Patent Deposit No. PTA-1644 under stringent conditions, said stringent conditions comprising hybridization in 6 X SSC at 42°C, followed by at least one wash in 1 X SSC at 55°C.

Please add new claims 44-56:

44. (New) The polypeptide of claim 19, wherein said polypeptide comprises the amino acid sequence set forth in SEQ ID NO:1.

45. (New) The polypeptide of claim 19, wherein said polypeptide comprises the amino acid sequence set forth in SEQ ID NO:3.

C4 46. (New) The polypeptide of claim 19, wherein said polypeptide comprises the amino acid sequence encoded by the cDNA insert contained in ATCC Patent Deposit No. PTA-1644.

47. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 80 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:2.

48. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 80 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:4.

49. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 90 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:2.

50. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 90 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:4.

51. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 95 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:2.

52. (New) The polypeptide of claim 29, wherein said polypeptide is encoded by a nucleotide sequence having at least 95 % sequence identity with the nucleotide sequence set forth in SEQ ID NO:4.

53. (New) A polypeptide comprising an amino acid sequence selected from the group consisting of:

a) a fragment of the amino acid sequence set forth in SEQ ID NO:1, wherein the fragment has phosphodiesterase activity and consists of at least 50 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:1;

b) a fragment of the amino acid sequence set forth in SEQ ID NO:3, wherein the fragment consists of at least 50 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:3; and

c) a fragment of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-1644, wherein said fragment has phosphodiesterase activity and consists of at least 50 contiguous amino acids of the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-1644.

54. (New) The polypeptide of claim 53, wherein said polypeptide further comprises heterologous amino acid sequences.

55. (New) The polypeptide of claim 53, wherein said polypeptide comprises a fragment of the amino acid sequence set forth in SEQ ID NO:1, wherein the fragment has phosphodiesterase activity and consists of at least 50 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:1.

56. (New) The polypeptide of claim 53, wherein said polypeptide comprises a fragment of the amino acid sequence set forth in SEQ ID NO:1, wherein the fragment has phosphodiesterase activity and consists of at least 50 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:3.

REMARKS

Status of the Claims:

Claims 19, 21, 29, 30, 32-35, and 44-56 are pending in the current application. Claims 2-18, 20, 22-28, and 36-43 have been cancelled without prejudice or disclaimer. Claims 19, 29, and 32-34 have been amended to correct minor informalities. New claims 44-56 have been added. Support for the new claims may be found in claims 1 and 2 as originally filed, as well as page 19, line 20 of the specification. No new matter has been added by way of amendment.

The Examiner is respectfully requested to withdraw the rejections and allow claims 19, 21, 22, 29-36, and 44-56. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were not made earlier because the Applicants earnestly believe that the specification is enabling for the breadth of the claims as originally drafted.

The Rejections U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 26, 27, 29, 30, 32-35, 37-39, 41, and 42 have been rejected on the grounds that the specification contains an insufficient description of the claimed subject matter. The rejection is respectfully traversed as applied to these claims as well as to the new claims for the reasons described below.

In rejecting the claims for inadequate written description, the Examiner argues that the Applicants have not described variants and fragments of the 22025 polypeptide and cites two cases, *In re Shokal*, 113 U.S.P.Q. 283 (C.C.P.A. 1957), and *Regents of University of California v. Eli Lilly and Company*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), in support of this

position. The Examiner quotes the court in *Shokal* in support of the argument that a single species can rarely be used to support a generic claim, however, the facts of the present case are readily distinguishable from those in *Shokal*. In *Shokal*, the specification filed by the Applicants did not define the claimed genus by identifying characteristics that would distinguish the claimed invention from other compounds. Instead, the Applicants attempted to establish possession of the claimed genus by the disclosure of representative species.

In contrast, the claimed genus in the present application is defined in the specification by the functional properties (*i.e.* phosphodiesterase activity) and the structural properties (*i.e.* sequence identity with disclosed sequences, hybridization with disclosed sequences, or deletions of disclosed sequences) shared by the encompassed species. This description is sufficient to distinguish the claimed genus from other materials. Accordingly, the disclosure of many species within the claimed genus is not required. Indeed, the court in *Shokal* makes this distinction, stating, "*where the genus is not set forth in express terms*, the number and nature of the examples given, together with the accompanying disclosure must be such as to indicate clearly what the genus actually is." (*Shokal* at 285, emphasis added).

The facts of the present case are also distinguishable from those in *Lilly*. In *Lilly*, the patentee had claimed a genus of nucleotide sequences based only on the function of the polypeptide encoded by the sequences. As described above, the present application defines the claimed genus by both the functional and structural properties of its members. In *Lilly*, the court stated:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus *or of a recitation of structural features common to the members of the genus*, which features constitute a substantial portion of the genus.

Lilly at 1569, emphasis added. Accordingly, claims 29, 30, 32-35, 44, and 45 meet the requirement for description of a genus of sequences set forth in *Lilly*.

Claims 29, 30, and 32-35, and 44-56 also meet the written description guidelines set forth in the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)). The guidelines state:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings...., *or* by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, *or* by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

66 Fed. Reg. 1106, emphasis added. In the present case, the recited sequences in claims 88-91 have been described by both their structural properties and functional characteristics, thereby meeting the standards set forth in the guidelines. The present claims are comparable to the claim presented in Example 14 of the "Synopsis of Application of Written Description Guidelines" cited in the written description guidelines (66 Fed. Reg. 1101), in which the claimed protein is described by its sequence identity with a second protein and by its function. In the analysis of this example in the Synopsis, it is concluded that the claimed polypeptide is adequately described. Similarly, in the present case the criteria for written description have been met and the rejection should be withdrawn.

Claims 19-21, 23, 24, 26, 27, 29, 30, 32-35, 37-39, 41, and 42 have been rejected under 35 U.S.C. § 112, first paragraph on the grounds that Applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention. The rejection is traversed as applied to these claims as well as to new claims for the reasons described below.

Claims 19, 29, 30, 32-34, and 44-52 recite isolated polypeptides having the amino acid sequence shown in SEQ ID NO:1, the amino acid sequence shown in SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-1644, as well as variants of the 22025 phosphodiesterase, wherein the variants have phosphodiesterase activity and are encoded by a nucleotide sequence that has a

designated level of sequence identity with SEQ ID NO:2 or SEQ ID NO:4, or a nucleotide sequence that hybridizes to SEQ ID NO:2 or SEQ ID NO:4 under stringent conditions. Claims 53-56 recite polypeptides comprising fragments of the 22025 amino acid sequence, wherein the fragments comprise 50 contiguous amino acids of the amino acid sequence shown in SEQ ID NO:1, the amino acid sequence shown in SEQ ID NO:3, or the amino acid sequence of the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-1644.

Sufficient guidance for making and using the claimed polypeptides is given in the specification. Applicants have provided the 22025 amino acid sequences of SEQ ID NO:1 and SEQ ID NO:3, and nucleotide sequences encoding these amino acid sequences. The polypeptides of claims 29, 30, 32-34, and 44-56 comprise subsequences of the amino acid sequences of claim 19 or amino acid sequences that are encoded by nucleotide sequences that differ from the disclosed 22025 nucleotide sequences by structural parameters (i.e. percent sequence identity to SEQ ID NO:2 or SEQ ID NO:4 or hybridization with the complement of SEQ ID NO:8 under stringent conditions) that are defined in the specification, and the claimed variants retain the phosphodiesterase activity of the 22025 polypeptide having the amino acid sequence set forth in SEQ ID NO:1, SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit Number PTA-1644. Guidance for determining percent sequence identity and hybridization under stringent conditions is provided in the specification (see pages16-17, land page 42, line 3 *et seq.*). Polypeptide sequence variants and fragments that retain function are also described in the specification as containing "only conservative variation or variation in non-critical residues or in non-critical regions" (page 18, lines 9-10 of the specification). Guidance regarding conservative substitutions of amino acids is found in the specification on page 15, lines 4-10 and Table 1.

Further, the 22025 sequences of SEQ ID NO:1 and SEQ ID NO:3 share a high level of sequence identity with a consensus domain that is conserved among members of the phosphodiesterase family of proteins (see figures 2 and 7). The specification also teaches methods for determining additional residues that are essential for function, including site-directed mutagenesis and alanine-scanning mutagenesis (page 18, line 29 *et seq.*).

Finally, the specification provides guidance regarding assays for phosphodiesterase activity on pages 2-5 of the specification. Accordingly, one of skill in the art would be able to determine the functionality of 22025 variants.

Thus, a rational scheme for determining the regions of the 22025 phosphodiesterase that would tolerate modification is provided. Based on the regions of the 22025 polypeptides that are conserved with other phosphodiesterases, and the methods provided for identifying additional residues critical for 22025 function, the skilled artisan could choose among possible modifications to produce polypeptides encoded by nucleotide sequences within structural parameters set forth in the claims and then test these modified variants to determine if they retain phosphodiesterase activity. Although some quantity of experimentation would be required, the level of experimentation would not be undue in view of the amount of direction provided in the specification, the state of the prior art, and the level of skill of one of ordinary skill in the art. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation.

In rejecting the claims for lack of enablement, the Examiner states that the claims are not limited to just those embodiments which exhibit phosphodiesterase activity. This statement is an inaccurate characterization of the claims. Claims 19, 21, and 44-46 are directed to polypeptides having the amino acid sequences given in SEQ ID NO:1, SEQ ID NO:3, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with ATCC as Patent Deposit No. PTA-1644. Applicants have demonstrated that these amino acid sequences share a high degree of sequence identity with phosphodiesterases as described above. Claims 29, 30, 32-34, and 47-56 specifically recite that the claimed variants and fragments have phosphodiesterase activity.

The Examiner also makes several bare assertions regarding the quantity of experimentation necessary to practice the invention, the nature of the invention, the state of the prior art but does support these statements by any evidence or arguments. For example, on page 5 of the Office Action dated August 21, 2001, the Examiner states, "[t]he quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success," but provides no support for this statement. Similarly, on

page 6 of the office action the Examiner states, "[t]he claimed invention relates directly to matters of physiology and chemistry which are inherently unpredictable and as such, require greater levels of enablement," but does not present any evidence to substantiate this argument. On page 7 of the Office Action the Examiner states, "[t]he state of the prior art has advanced to the point where the unpredictable nature of proteins is more commonly recognized," but does not provide a single reference to demonstrate that this is the view of those of skill in the art.

The statements in the Office Action regarding the enablement of the present claims are at odds with the case law, which supports a conclusion of sufficient enablement when claims are restricted to functional variants and a rational scheme for identifying functional variants is available. *See, e.g., Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. 1989). In *Mark*, the Board determined that appealed claims directed to cysteine-depleted muteins that required the mutein to retain the biological activity of the native protein, were enabled. *Id.* at 1906-07. The Board found that the record established that for a given cysteine-containing protein, one skilled in the art would be able to determine in a routine fashion whether replacement or deletion of a cysteine residue would result in a mutein that retained the biological activity of the native protein. *Id.* at 1906-07.

Statements made by the Federal Circuit in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* (927 F.2d 1200, 18 USPQ2d 1016 Fed. Cir. 1991) regarding the enablement requirement for sequence variants are consistent with the finding of *Mark.* In *Amgen*, the Federal Circuit repeatedly turned to the fact that Amgen tried to claim all analogs of the EPO gene. The court emphasized the point that generic claims to variants are possible as long as they are not overly broad:

> In affirming the district court's invalidation of [the relevant claims] under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

Id. at 1214. The statement by the court supports the argument that where claims to nucleotide sequence variants contain both structural and functional limitations, and the specification

provides sufficient guidance for one of skill in the art to make and use variants meeting these limitations, the enablement requirement has been met.

In the instant case, claims 29, 30, 32-34, and 47-56 specify that the claimed nucleic acid molecules comprise nucleotide sequences encoding polypeptides having phosphodiesterase activity, thereby imposing a functional limitation on the claimed sequences. The claims additionally state that the claimed polypeptides comprise a subset of the disclosed amino acid sequences or are encoded by nucleotide sequences that share a given level of sequence identity with the disclosed 22025 nucleotide sequences; or hybridize with these nucleotide sequences under stringent conditions. A scheme for identifying fragments and variants meeting the functional and structural limitations of the claims is given in the specification as demonstrated above. Accordingly, the invention of claims 19, 21, 29, 30, 32-34, and 44-56 meets the standard for enablement set forth in the applicable case law.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection Under 35 U.S.C. § 101 Should be Withdrawn

Claims 19-21, 23, 24, 26, 27, 37-39 41, and 42 were rejected under 35 U.S.C. § 101 on the grounds that they lack utility. The rejection is respectfully traversed as applied to these claims as well as to the new claims. The Examiner states that the claims are rejected on the grounds that they encompass polypeptides that lack phosphodiesterase activity; however, as discussed above in regard to the rejection of the claims under 35 U.S.C. § 112, first paragraph, claims 19, 21, and 44-46 are directed to polypeptides that have been demonstrated to function as phosphodiesterases and claims 29, 30, 32-35, and 47-56 specifically recite that the claimed polypeptides have phosphodiesterase activity. Accordingly, the rejection under 35 U.S.C. § 101 should be withdrawn.

CONCLUSION

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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